Effect of Restricted Feeding Upon Aging and Chronic Diseases in Rats and Dogs*

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IN our modern age of nutrition the theory has been dominant that the body should be supplied with an excess of essential nutrients from the cradle to the grave. We have attempted to force the growth of animals such as chickens, swine, babies, and puppies to the maximum. We have read of balance experiments, run with inorganic elements such as calcium, in which the maximum need was indicated by the data itself. Then we have observed nutrition students increasing this level in establishing a so-called "limit of safety." We have also read experimental evidence that an animal did not store calcium in maximum capacity during growth or that a lactating animal failed to maintain a balance of calcium during the early months of lactation. Invariably, authors have concluded that such conditions were defects within the metabolism of the animal and that our goal should be to correct these defects.

On the other hand, little attention has been given to possible advantages of the ingestion of low levels of nutrients during at least certain periods of the life cycle of men and animals. Many factors have undoubtedly shaped this philosophy of nutrition. The outstanding one has probably been the short-time character of most experiments. To date most research studies have considered only a brief fraction of the total span of life of men or animals. Except in special areas, such as that concerned with efficiency in the performance of work or in the resistance to diseases of bacterial origin, short-time studies give little evidence of possible interrelationships between the level of ingestion of nutrients and the performance of an animal or man during the whole span of life.

Inasmuch as nutrition research has made many of its advances in the course of studying farm animals, it tends to have its philosophy colored by these investigations even when the results are applied to human beings. In rearing farm animals such as swine, poultry, and beef cattle, for meat the factor of dominant importance is always the cost in terms of feed and labor to produce a pound of human food. Under most conditions the more rapidly an animal grows, the more efficiently it converts feedstuff into body tissues. Inasmuch as most meat producing animals are slaughtered before they have completed more than a third of their total span of life, little attention is paid to any factor other than a feeding program that will maintain health and efficient conversion of feedstuffs until the time of slaughter.

However, recent studies in England have devoted considerable attention to the alteration in anatomical structure of farm animals by severe restriction of

* Presented before the Food and Nutrition Section of the American Public Health Association at the Seventy-fourth Annual Meeting in Cleveland, Ohio, November 12, 1946.

essential nutrients during the growing period.[1] These afford interesting possibilities for complementary action between the inheritance of body structure and modifications during growth. In last analysis, however, the practical use of such studies depends upon the efficiency of conversion of nutrients into meat.

Human beings, however, are supposedly reared for the purpose of optimum productivity during a whole span of life.

This brief discussion of farm animals is introduced by way of contrast in order to define sharply our thinking in regard to objectives. In one case we are converting feedstuffs into meat; in the other we are attempting to produce human beings who can enjoy optimum health and hence perform a maximum of useful work during the whole span of life.

In order further to clarify our philosophy, brief consideration should be given to our major objective in research in the field of aging or gerontology. The opinion is rather general that researchers are attempting to drag out the period of decrepit old age with its resulting vast economic burden due to illness and dependence. Quite the opposite is the case, since the objective of research upon aging is the discovery of ways of maintaining optimum health during the declining years of the life span so that this burden due to dependence will be alleviated.

From this introduction it might seem that applied agriculture has little interest in research in gerontology other than that the farm population must bear its share of the burden of the aged who become ill so they cannot carry their portion of farm labor. This is not entirely true since it is economically important for certain classes of livestock to have a long adult life. In different parts of New York State the average dairy cow has a productive life of only 5 to 7 years. However, the potential productive life of the cow is about 20 years. In this case a long productive life is economical. In fact, one group of Jersey and Guernsey breeders have favored a restricted diet during growth for these two breeds of cows in order to produce the best types and the most productive animals. Like the Shetland pony, these breeds originated on islands where the limited supply of food retarded the growth and restricted the ultimate body size.

LOW ENERGY DIETS

For centuries there are records of individuals, religious sects, and geographical areas in which people from choice or necessity passed much of their lives upon diets that barely prevented starvation. One of the greatest advocates of such nutrition was Luigi Cornaro (1464–1566). His book passed through a number of editions and was published in America in 1917 under the title of *Art of Long Living*. He advocated a very simple diet of about 14 ounces of food per day. This consisted of soup, bread, and an egg each day, with a small addition of meat for those who could afford it. Of course, Cornaro drank wine instead of water with his simple diet.

One can find other records of such human diets. However, we can draw few satisfactory conclusions about results because we know too little about the quality of the food and the many other variables that influenced the lives of these men. From the viewpoint of modern nutrition it seems difficult to understand how men like Cornaro survived. It is equally difficult to understand how the poor of many lands have lived for centuries upon simple diets. When we add together the twenty-five to fifty vitamins, fatty acids, inorganic elements, and amino acids that are recognized today as essential constituents of human food, it is almost

unbelievable that survival was possible, especially after men started to process and destroy natural foods.

This complex problem of providing a diet in minimum amounts that will provide optimum levels of all essential nutrients has been stressed because it is a matter of supreme importance to basic research in animal experiments. Until modern times the effects from both human experience during periods of famine, and of animal experiments in the laboratory in feeding low energy diets, were confused because such diets under both conditions were usually deficient, not only in calories but in numerous other essentials such as proteins, calcium, and vitamins.

Before proceeding with a brief discussion of controlled experiments with animals, it may be well to review one of the outstanding records of human experience, namely the studies of Chadwick.[2] Edwin Chadwick (1800–1890) is best known as a lawyer-sanitarian who pioneered in England a century ago in the improvement of sanitation, housing, education, and factory labor conditions. Even today most of us can well afford to have constantly before us for rereading, the great works of Chadwick edited by B. W. Richardson under the title of the *Health of Nations*.

Chadwick's contributions to our knowledge of low energy diets resulted from a comparative survey of prison diets used in England. His study was made in coöperation with the statistician William Farr in the years 1830–1832.

Due to the diversity in food allowed in the 128 prisons under study it was found that these prisons could be divided into three classes. In one only 128 ounces of solid food were allowed per week, in the intermediate class the allowance was 213 ounces, and in the highest 218. These two latter were close together on amounts but differed considerably in the money expended. At this period in England, agricultural laborers consumed only 122 ounces of food weekly. Unfortunately we cannot calculate these diets into modern terms of proteins, fats, etc.

The outstanding results of this study were the much lower death rates in the prisons using the lowest food allowances in comparison with the other two. Chadwick concluded, "The average excess of sickness which was the concomitant of the excessive forms of dietary, amounted to no fewer than five thousand eight hundred and eighty-two cases per annum, yielding an unnecessary mortality of ninety-four." Although there is no mistaking the conclusions of Chadwick it is difficult to fit them to the meager data upon illness cited by Richardson. If the original data were available it would be interesting to repeat the calculations using modern methods.

Inasmuch as we have reviewed the literature elsewhere in the limited field of animal research dealing with the interrelationships between restricted diets, growth rate, and the diseases of old age, we will only consider a few earlier works at this time.[3] Jackson has provided thorough reviews upon the general subject of inanition.[4]

One of the earlier studies, that have been forgotten in modern times is that of Moreschi.[5] He extended earlier British observations indicating that restriction of foods slowed or prevented the growth of tumors in animals. In his studies with mice Moreschi transplanted tumors and followed their rate of growth. He found the tumor grew in relation to the amount of food allowed the animal. Mice fed on restricted diets lived longer. Under some conditions of restricted diet he found it difficult to transplant tumors.

These original findings of Moreschi which have been rediscovered in modern times were probably neglected because Rous made a similar study with rats[6]

and failed to get any effect from restriction of the diet. In the report of Rous, there is no evidence, however, that the results of Moreschi with mice were in question.

In addition to interest in diseases in the study of restricted diets, another outstanding problem concerns the ability of an immature animal to resume growth after long periods of retardation. For nearly twenty years we have given attention to this problem, using several species, namely, the dog, the rat, and the brook trout.

Although the use of restricted diets offers vast opportunities in the modification of types within breeds of dogs, little attention has been given to this subject. In 1911, Aron[7] reported a few studies with mongrel puppies in which he retarded the growth by the restriction of food. Under such conditions he found that the skeleton continued its growth to a limited extent. After a puppy was restricted for 350 days it seemed to have lost its ability to resume growth and attain a normal size.

In two preliminary studies using dogs of known breeds we have extended this work.[8,9] In the first, a litter of five Saluki pups was used. Three of these were allowed to grow normally and two were retarded until 440 days of age with the restricted diet starting when the pups were 3 months old. The growth of the tibia in each pup was followed by means of x-ray photographs made at regular intervals. There was slow growth of the bones during the first 300 days of the study. After re-alimentation there was no evidence that the retarded pups could attain the size of the control animals.

Dr. W. T. James made a number of studies upon these dogs to determine if there were differences in rate of learning. He found none. He did find a lower heart and breathing rate in the retarded dogs. When required to perform a given amount of work such as walking there was obviously a greater strain on the body of the underfed. Housed in a warm kennel, but provided with an outdoor run, these Salukis, which are naturally as thin as greyhounds and have limited hair protection, survived a cold winter.

A second experiment was completed just prior to the war using three long haired terrier puppies from a Scotch-Cairn cross. Two of these were females and one was a male. When 65 days old the male and one female puppy were started upon a restricted diet designed to provide an adequate intake of all essential nutrients except energy, even when fed at maintenance levels. The other female puppy was given all the food desired.

All puppies weighed 4 pounds at the start of the study. At the age of 357 days the two retarded animals weighed slightly more than 9 pounds each, while the control weighed 15. Re-alimentation started at that time. At the conclusion of the study when the pups were 374 days old, the control female and the retarded male weighed 15 pounds while the retarded female weighed 13.5 pounds. Careful measurement of the leg and head bones indicated that the size of the skeleton was proportional to the body weight.

Both of these preliminary studies with dogs confirm the findings of Aron that if dogs are maintained upon restricted diets so that growth is retarded for a period of a year, the animal loses its power to attain full adult size. In the second study the pups were kept in unheated kennels and had no difficulty in surviving a cold winter. The retarded pups were exceptionally active and alert. Contrary to normal dogs they were so hungry that they would eat dog meat if offered them. Thus hunger drove them to cannibalism.

STUDIES WITH WHITE RATS

Some of the finest papers of the late

Professor L. B. Mendel were concerned with the problem of the suppression of growth and the capacity to grow.[10] He was able to retard the growth of rats for more than a year. In one case he kept a rat on a restricted diet for 532 days and found it still retained the capacity to grow. Since Mendel's work in 1914, advances in our knowledge of nutrition have permitted the design of superior diets. Today we can feed mixtures enriched in essential nutrients so that we are more certain of providing for needs of the body if we wish to restrict the growth by limiting the energy intake.

Of course we can never be sure of the ultimate limiting factor under such conditions. When calories are severely restricted, the body may utilize essential amino acids or even vitamins for fuel. Hence these may be the ultimate units that prevent normal growth.

Since 1930 our studies upon aging in rats have been of three types: In the first we have retarded rats for long periods and determined the effects in terms of diseases that developed and the total span of life.[11] In the second we have introduced dietary variables in the middle of the life span when rats were about a year old.[12] In the third, various attempts have been made to improve normal human diets by the addition of natural foods.[13]

Three long series of these restricted diet studies have been completed since 1930. All have given similar results. Rats long retarded by diets with excess of recognized essential nutrients, but inadequate in energy allowance to permit growth, far exceed the normal span of life for their species. The oldest rat thus far lived 1,456 days, while the normal span of life for a white rat is about two years.

The growth impulse of rats maintained upon restricted diets for long periods persists strongly for 900 days. After this it tends to decline and is lost in various individuals. In one case it persisted in a rat for 1,150 days. When such rats are re-alimented and resume growth even after 900 days they always fall short of attaining the adult size that would have been achieved if they had grown normally from an early age. Thus, in one series of studies the length of the tibia varied from 3.8 to 4.1 cm. for normal adult males, while the mean lengths for those retarded 300 and 900 days respectively were 3.7 and 3.5 cm.

Of all the organs and tissues of the body the bones seem the most persistent in maintaining their growth. Likewise, in retarded animals the bones seem to persist in the deterioration of old age through the loss of inorganic materials. Thus they become thin and fragile or we may say "old" in rats prevented from attaining adult size beyond their normal span of life. At the same time these bones are aging, other parts of the body such as the hair maintain their youthful character.

From our earliest studies it was evident that the retardation of growth upon diets of excellent quality, but restricted in amount, resulted in a long span of life because the retarded rat was less subject to the usual terminal diseases that start in the second year. Thus in the first series of studies made in the early '30's no tumors were observed among retarded rats until after they were allowed to grow. On the other hand, about 12 per cent of the rats allowed to develop normally had tumors. However, the organ that seems to fail first in rats is the lung. Second to this organ are probably the kidneys. In old age the rat seems to have little trouble with the heart and blood vessels.

In the first two series of retarded growth studies only limited attention was paid to pathology. In the course of this research it became evident that teamwork between nutrition and pathology afforded the most effective method devised thus far for attacking the

problem of chronic diseases of old age.

The third large study started in 1939 and involved 500 rats. Some of these were killed at regular intervals, in order to follow the development of chronic diseases. Dr. John A. Saxton, Jr., has published a number of summaries of observations upon these rats.[14] He has found that the chronic pneumonia which seems to terminate the lives of most old rats, develops much more slowly in those fed restricted diets and thus retarded in growth. The elasticity of the lung tissue seems to be better maintained in these underfed animals.

In order to penetrate still further behind the pathological picture, Dr. O. H. Lowry and associates[15] have attempted to apply histochemical methods to the study of the tissues of some of these rats. They found the kidney tissues afforded most evidence of changes with age. They believed the restriction in calories may have favored this organ in keeping it younger in retarded animals. Inasmuch as the daily ingestion of proteins, vitamins, and inorganic constituents was kept the same for all rats, the aging of or injury to the kidneys in normal rats could not be referred to any of the classical reasons such as a difference in the amount of nitrogen excreted daily. This burden was the same for all animals. Hence the kidney changes must have been associated with aging. However, in this case the retarded animals seemed to have maintained "younger" kidneys just as they did more elastic lungs.

The restriction of calories during the latter half of life is also effective in extending the total span of life of the rat just as it is in the case of man.[12] However, this extension is small compared to that resulting from severe limitation of calories during the growing period.

Little research has been directed toward either restriction of special nutrients or the effect of specific excesses upon the diseases of old age. Kon has indicated that the absorption of calcium declines in old age,[16] so that the allowance should probably be increased. However, Shields and Mitchell[17] have found no evidence that higher levels of calcium in the diet extend the span of life of rats. It is probable that Kon was concerned with a border-line allowance of this element while Mitchell's lowest level made adequate provision for the needs in old age even with a decreased absorption rate.

In our own laboratories we have had experiments in progress during the past few years[11] in an attempt to answer three questions:

1. Will a moderate consumption of coffee equal to a cup per day for man modify the life span?
2. Can the typical diet consumed in the northeastern part of the United States be improved by supplementation with vitamin concentrates?
3. Can this diet be improved by changes suggested by modern nutrition such as the use of more organ meats, whole wheat bread, and milk?

These experiments have been described in detail elsewhere,[11] but the results can be expressed here in a few words. As far as the life span of the white rat can serve as a criterion, there is no evidence of improvement in this average human diet either by supplements of vitamins or by increases in such foods as liver, milk, and whole wheat bread. Furthermore, there is no evidence of modification of the life span from the daily ingestion of a moderate amount of coffee beverage. In fact, two groups of rats indicated significantly favorable responses to this beverage.

Following this study, small groups of rats were forced to consume no other beverage than coffee from the time of weaning. This study now has reached its third generation. In other words, two generations of rats have grown to maturity, reproduced and reared young,

with coffee to drink instead of water. The growth rates of the rats were slightly slower, but they attained the same adult size and seemed to have no trouble in reproduction. This study has not been extended to a consideration of the life span.

At present we are starting a new series of experiments to determine whether the daily ingestion of large amounts of fluid will tend to preserve the kidney against age changes in the rat. One of the variables in this study will be coffee. Another will be liquid milk. A technique has been devised by which the rat can be induced to consume three to five times as much water as it drinks normally. This technique is the same as that used previously in studying the effect of acid beverages upon teeth.[18] It makes use of the fact that a rat will drink much more of a solution containing 10 per cent sucrose than it will of water. The outcome will be known about four years from now.

SUMMARY

The purpose of all research upon aging is to find means of alleviating the chronic diseases of old age. Thus we can look forward to more productive years and less financial dependence in man. Severe restriction in food intake has long been advocated by individuals and certain sects. It has been essential in many nations. Until modern times, however, such restriction has had attendant risks since we were unfamiliar with numerous essentials that must be included in diets.

Studies with dogs and rats covering the past sixteen years have been reviewed. Puppies can be severely retarded in growth by restriction of food. They seem to suffer no ill effects in the course of a year even when kept in cold kennels during the winter. However, such puppies do not attain normal body size even when the restriction is maintained for only a year.

Three long-time experiments in maintaining rats during the growing period upon diets adequate in known essentials except calories indicate that the life span is much extended. This is due in part to the slower development of chronic diseases of the lungs in rats whose growth is retarded by diets low in energy value. Such diets and such slow growth also lead to a much lower incidence of tumors and possibly to less aging of special organs such as the kidneys and lungs.

Under conditions of restricted diets, bones seem to be the most persistent in their growth. However, rats, like puppies, retarded for even 300 days cannot attain normal adult size. However, rats seem to have more ability than other species to resume growth after long periods of suppression.

A few recent studies indicate that excess of special food substances does not succeed in extending the life span of rats by supplementing a normal human diet with either vitamins or by means considered especially worth while, such as additions of liver, whole wheat bread, and more milk. The ingestion of moderate amounts of coffee as a beverage had no unfavorable effect upon the life span of rats. New studies are under way in which the amount of liquid ingested daily is the principle variable.

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